



# Is high-dose fluticasone propionate via a metered-dose inhaler and Volumatic<sup>TM</sup> as efficacious as nebulized budesonide in adult asthmatics?

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The efficacy and tolerability of fluticasone propionate (FP) 2 mg daily via a metered-dose inhaler and Volumatic<sup>TM</sup> (GlaxoWellcome) spacer device was compared with nebulized budesonide (nBUD), 2 and 4 mg daily, in a multi-centre, open-label, cross-over study of adult asthmatics. Patients received, in random order, either 4 weeks of treatment with FP followed by 4 weeks of treatment with nBUD, or *vice versa*, with an intervening 4 week 'wash-out' period between treatments. Thirty patients completed the study, of whom 24 were evaluable. In terms of the primary efficacy parameter, change in mean morning peak expiratory flow (PEF) ( $\text{l min}^{-1}$ ) from baseline to the fourth week of each treatment period, FP was more effective than nBUD [mean difference (FP – nBUD)  $21.1 \text{ l min}^{-1}$ ,  $P=0.007$ , 95% CI (6.5, 35.7)]. Sub-group analysis demonstrated FP to be superior to the 4 mg nBUD [mean treatment difference (FP – nBUD)  $42.9 \text{ l min}^{-1}$ ,  $P=0.026$ , 95% CI (7.1, 78.8)] and at least as efficacious as the 2 mg nBUD sub-group [mean treatment difference (FP – nBUD)  $10.2 \text{ l min}^{-1}$ ,  $P=0.211$ , 95% CI (–6.5, 26.9)]. Furthermore, larger reductions in diurnal variation were observed during FP treatment [mean treatment difference (FP – nBUD) –4.4 percentage points,  $P=0.028$ , 95% CI (–8.4, –0.5)]. There was no significant difference between the treatments for the proportion of symptom-free 24 h periods. Of those expressing a preference, significantly more patients found FP via a metered-dose inhaler and spacer device both easier to administer (78%,  $P=0.007$ ) and more convenient to take (76%,  $P=0.008$ ) than nebulized budesonide. In addition, cost per patient analysis showed that nebulized budesonide was from 1.7 to 3.5 times more expensive than FP.

RESPIR. MED. (1998) 92, 111–117

## Introduction

Nebulized budesonide (nBUD) is the only nebulized corticosteroid currently available in the U.K., and is licensed at a higher dose than either the aerosol or dry powder formulations of budesonide. It is used by a minority of severe asthmatics whose disease is difficult to control. There is some evidence to suggest its use may reduce the need for oral steroids (1,2).

However, this mode of delivery suffers the disadvantages of inconvenience and portability. In addition, several studies have demonstrated a wide variation between different compressor/nebulizer combinations in the flow rate and

particle size produced, which is a major determinant of the amount of drug made available to the lungs (3–5). To date, there have been no studies comparing the efficacy of high-dose inhaled corticosteroids when delivered via a nebulizer or the more commonly used and convenient metered-dose inhaler (MDI) and spacer device. Fluticasone propionate (FP) is the most recently introduced inhaled corticosteroid available for the treatment of asthma. Studies using MDIs and powder inhalers comparing FP with both budesonide and beclomethasone dipropionate have shown, over a range of doses, that FP is as efficacious as the older corticosteroids, when administered at half the microgram dose (6–12). FP is licensed for use in adults up to a dose of 2 mg daily, thus enabling patients to receive what is, in effect, a higher dose of inhaled corticosteroid via the more commonly used delivery devices, than was possible previously (13).

This study aimed to compare the efficacy and tolerability of inhaled FP 2 mg daily via an MDI and Volumatic<sup>TM</sup> (GlaxoWellcome) spacer device with nBUD (2 and 4 mg

Received 23 January 1997 and accepted in revised form 27 October 1997.

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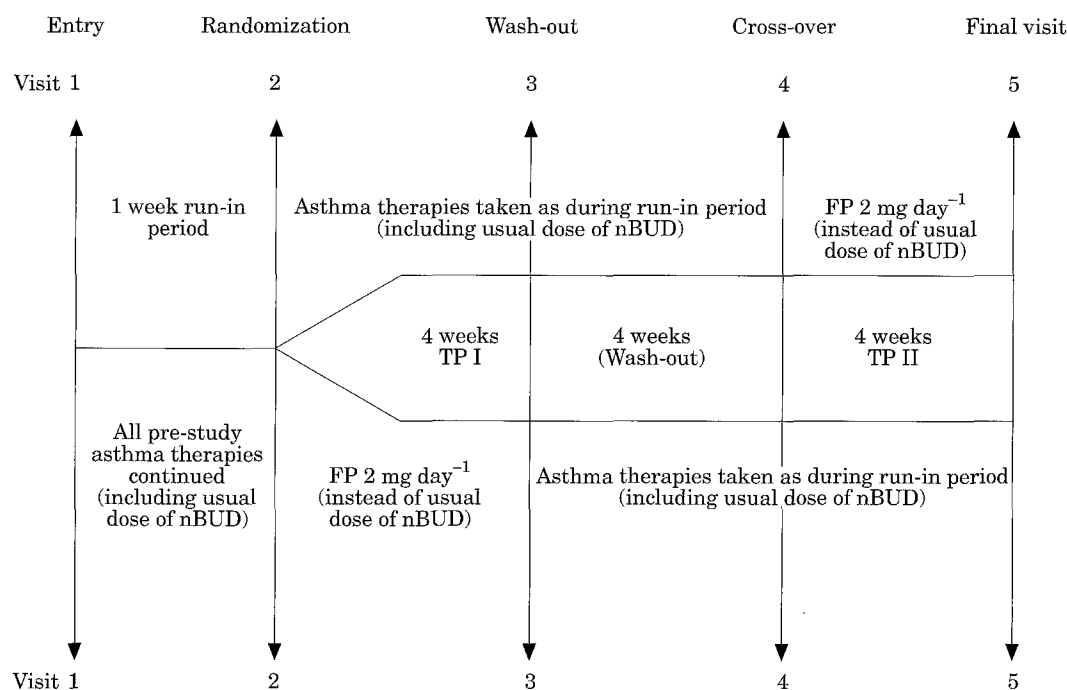


FIG. 1. Study plan. TP, treatment period; FP, fluticasone propionate via a metered-dose inhaler and Volumatic<sup>®</sup> spacer device; nBUD, nebulized budesonide. Notes: 1. During FP treatment, only nBUD was stopped; all other asthma therapies as taken during the run-in period were continued. 2. The patient's usual dose of nBUD was either 2 or 4 mg daily.

daily), to determine whether FP can provide an alternative to regular nBUD therapy, in those patients already using nBUD as part of their maintenance regimen.

## Patients and Methods

### PATIENTS

Patients aged 18–70 years inclusive were eligible to enter the study if they had documented evidence of long-term asthma, demonstrating a typical clinical pattern of marked variability in symptoms and significant (>15%) variability and reversibility of peak expiratory flow (PEF) to bronchodilators, and/or PEF variability. Patients had to have been using nBUD regularly, and for the 4 weeks immediately preceding the study, at a daily dose of either 2 or 4 mg. Patients were also required to be using their nebulizer for regular bronchodilator therapy at entry and over the preceding 4 weeks. Patients were excluded if they were taking any other inhaled corticosteroid by any other device, or had done so during the preceding 4 weeks, or had suffered an exacerbation of their asthma requiring hospitalization during this period. Current regular smokers (defined as greater than five cigarettes per day) were also excluded. Patients were allowed to be on maintenance oral corticosteroids, but the dose had to remain constant for them to be included in the efficacy analysis.

The study was approved by an ethics committee local to each participating centre, and written informed consent was obtained from each patient prior to entry.

### STUDY DESIGN

This was a multi-centre, open-label, randomized cross-over trial conducted in 10 hospital and General Practice centres. A summary of the study plan is shown in Fig. 1. After a 1 week run-in period, during which patients took their usual asthma medication, including their usual dose of nBUD (2 or 4 mg daily), patients were randomized to Treatment Period 1. One group received FP 1 mg b.i.d. via a MDI and Volumatic<sup>®</sup> spacer device instead of their usual nBUD (continuing all other asthma therapies), whilst the second group continued to receive all their usual asthma therapies, including their usual dose of nBUD. After 4 weeks, all patients then entered the wash-out period during which they took the same asthma medications as during the run-in, for a further 4 weeks. The two groups then crossed over such that the first group received their usual dose of nBUD whilst the second group received FP instead of nBUD, for the final 4 weeks of the study (Treatment Period 2). Patients were allowed to extend the wash-out period, by a maximum of 4 weeks, if they had altered any of their asthma medications, and could continue in the study provided that their asthma medications in the 4 weeks immediately preceding Treatment Period 2 were the same as during the run-in period.

Withdrawal was at the discretion of the physician or at the request of the patient.

## ASSESSMENTS

During the run-in, wash-out and treatment period, patients kept a daily record of their morning and evening PEF rates, daytime and night-time symptom scores and whether or not they had symptoms on waking. At the end of the study, patients were asked which of the two treatments they preferred. Adverse events were recorded at visits 2–5 inclusive.

## STATISTICAL METHODS

### *Efficacy and Device Handling*

The primary efficacy parameter was changed from baseline (or wash-out for Treatment Period 2) in mean morning PEF. Based on at least 90% power to demonstrate FP 2 mg daily was at least as effective as nBUD (2 or 4 mg daily) with 95% confidence intervals, a maximum acceptable clinical difference of  $151 \text{ min}^{-1}$  in favour of budesonide, and assuming a residual standard deviation of  $251 \text{ min}^{-1}$  from analysis of covariance (ANCOVA), it was calculated that 15 evaluable patients would be required in each sequence group, a total of 30 patients.

The primary efficacy parameter and the two secondary efficacy parameters, daily diurnal variation and proportion of symptom-free days, were analysed using the efficacy sample of patients. This sample included all randomized patients who completed at least 4 weeks of each treatment period, and who did not take additional oral steroid medication for the treatment of an asthma exacerbation during the treatment periods. Daily diurnal variation (DV) was calculated based on the following formula:

$$\text{DV}\% = 100 \times \frac{(\text{maximum} - \text{minimum})}{\text{maximum}}$$

(of the morning and previous evening PEF)

For each patient, the mean morning PEF ( $1 \text{ min}^{-1}$ ), the mean daily diurnal variation (%), and the proportion of symptom-free 24-h days were calculated over the last 7 days of each study period. In addition, each patients' changes from baseline were also calculated for all of these parameters. ANCOVA, appropriate for a cross-over design (14), was used to compare the two treatments in change from baseline in mean morning PEF and diurnal variation. The stratification variable, total daily dose of nBUD (2 or 4 mg) at study entry, was included as a covariate in the model. Due to evidence of a treatment difference which varied according to nBUD dose for change from baseline in mean morning PEF, additional treatment comparisons for this parameter were carried out for each of the two dose strata subgroups (2 and 4 mg) separately. No other parameters were affected significantly by this interaction. The statistical comparison of the changes in symptom-free 24-h days was performed using the permutation test, using

the actual change from baseline data as the scores. Device preference data were analysed using the Mainland-Gart test for all patients who completed both treatment periods.

All statistical tests were two-sided, and the significance level was taken as 5%. For all efficacy analyses, the baseline and wash-out values were incorporated into the test for carry-over and treatment by period interaction effects. Statistical analysis was carried out using PC SAS version 6.08 and StatXact Turbo version 2.11.

### *Cost Analysis*

The total number of days that study medication was used during the two study treatment periods was determined for each patient, and this was multiplied by the daily cost of the medication, calculated from the unit cost as defined in the British National Formulary (September 1995 edition). For nBUD, the cost was based on  $500 \mu\text{g ml}^{-1}$  Pulmicort Respules<sup>®</sup> (Astra) in a  $20 \times 2 \text{ ml}$  unit pack (£44.64), and for FP, the costs were based on 250  $\mu\text{g}$  doses in a 120-dose Flixotide<sup>®</sup> (GlaxoWellcome) (£38.86). Patient costs for FP and nBUD were totalled separately for the patients on 2 and 4 mg nBUD. These total costs were then divided by the number of patients to provide a cost per patient for each drug. The relative costs of FP compared with nBUD 2 and 4 mg doses, were also calculated.

## Results

### STUDY POPULATION

Thirty-seven patients were randomized to the study in total (the intention to treat sample), 19 to sequence Group A (FP 1 mg b.i.d. followed by nBUD) and 18 to sequence Group B (nBUD followed by FP 1 mg b.i.d.). Seven patients withdrew after randomization, six of whom withdrew due to adverse events. The seventh patient asked to be withdrawn after completing the first treatment period on FP as she wished to continue on this treatment due to improved asthma control. Five of the adverse events reported were asthma exacerbations (four occurred in the wash-out period and one in Treatment Period 2 whilst on FP) and the sixth was a headache (FP, Treatment Period 2). Of the 30 patients completing the study, a further six were excluded from the analysis; three took extra medication for a deterioration in their asthma control (all whilst on nBUD, one during Treatment Period 1 and two during Treatment Period 2), one patient reduced the dose of oral corticosteroids (for arthritis), and for two patients, no diary data were available. Thus, 24 patients were included in the efficacy analysis, 12 in each sequence group. Of these 24 patients, 16 were taking 2 mg daily and eight were taking 4 mg daily. The demographics and asthma history of the efficacy sample, by sequence group, are shown in Table 1. Asthma history is also shown by nBUD dose, together with concurrent asthma medications, in Table 2. Values for the lung function parameters at the baseline of each treatment period are shown for the efficacy sample in Table 3. These data show that the baseline mean morning PEF was similar

TABLE 1. Demography and asthma history – efficacy sample

	Sequence Group A (FP→nBUD) (n=12)	Sequence Group B (nBUD→FP) (n=12)
Sex		
Females	5 (42%)	6 (50%)
Males	7 (58%)	6 (50%)
Age (years)		
Mean (SD)	51.5 (9.4)	50.2 (13.0)
Range	28.0–63.0	28.0–67.0
Duration of asthma (years)		
Mean (SD)	25.4 (16.3)	26.3 (15.9)
Range	1.5–53.0	6.0–53.0

TABLE 2. Asthma duration and concurrent asthma medications at entry by nebulized budesonide dose – efficacy sample

	2 mg nBUD (n=16)	4 mg nBUD (n=8)
Asthma medications		
No. of patients (%)		
Salbutamol	10 (62.5)	6 (75.0)
Terbutaline	8 (50.0)	4 (50.0)
Anti-cholinergics	14 (87.5)	7 (87.5)
Xanthines	10 (62.5)	4 (50.0)
Salmeterol	6 (37.5)	3 (37.5)
Cromoglycate	1 (6.3)	0 (0.0)
Prednisolone	5 (31.3)	4 (50.0)
Methotrexate	1 (6.3)	1 (12.5)
Duration of asthma (years)		
Mean (SD)	26.9 (15.60)	23.9 (17.1)

before both study treatments, and not significantly different between the two nBUD dose groups. The baseline mean diurnal variation was also similar before both treatments,

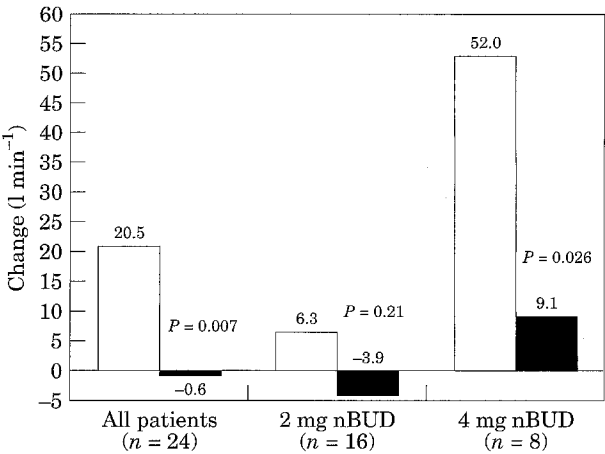


FIG. 2. Mean change from baseline in patient's mean morning peak expiratory flow (PEF) ( $\text{l min}^{-1}$ ) – efficacy sample. Open bars, FP; solid bars, nBUD.

but was lower in the 4 mg nBUD patients than in the 2 mg nBUD patients.

PRIMARY EFFICACY PARAMETER

The mean change from baseline in mean morning PEF are shown in Fig. 2. Overall, whilst there was little mean change observed during treatment with nBUD, improvements were observed during treatment with FP. Eight patients did improve more whilst receiving 2 mg nBUD compared with FP. All these patients were on different nebulizer/compressor combinations, and so this improvement cannot be attributed to a particular type of equipment.

The mean and 95% confidence intervals for the treatment difference (FP–nBUD) in change from baseline in mean morning PEF are shown in Fig. 3, with individual patient data plotted alongside. Overall, the mean treatment difference was  $21.11 \text{ min}^{-1}$  in favour of FP which was statistically significant ( $P=0.007$ ). for the 2 mg nBUD sub-group, the treatment difference was  $10.21 \text{ min}^{-1}$  ( $P=0.21$ ), and for the 4 mg nBUD sub-group,  $42.9 \text{ l min}^{-1}$  ( $P=0.026$ ). These data show that overall and in the 4 mg

TABLE 3. Summary of lung function at the baseline for each treatment period – efficacy sample

	Pre-FP			Pre-nBUD		
	All (n=24)	2 mg nBUD (n=16)	4 mg nBUD (n=8)	All (n=24)	2 mg nBUD (n=16)	4 mg nBUD (n=8)
Mean morning PEF ( $\text{l min}^{-1}$ )						
Mean	266.0	269.2	259.7	264.2	262.6	267.4
(SD)	(73.1)	(71.1)	(81.6)	(67.5)	(60.1)	(84.8)
DV (%)						
Mean	12.9	14.1	10.5	12.4	13.7	9.8
(SD)	(9.4)	(9.9)	(8.5)	(7.8)	(8.1)	(7.1)

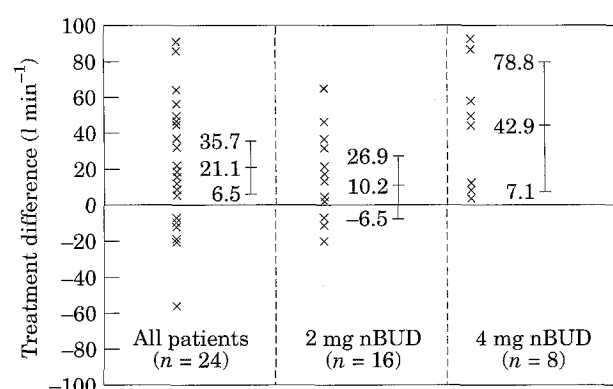


FIG. 3. Individual patient data, mean and 95% confidence intervals for the estimated true treatment difference (FP-nBUD) in change from baseline in mean morning PEF ( $\text{l min}^{-1}$ ) – efficacy sample.

TABLE 4. Mean change from baseline in patients' diurnal variation (percentage points) – efficacy sample

	Change from baseline in DV (p.p)	
	After FP treatment	After nBUD treatment
All ( $n=24$ )	-3.4	1.1
2 mg nBUD sub-group ( $n=16$ )	-4.4	1.5
4 mg nBUD sub-group ( $n=8$ )	-1.4	0.5

nBUD sub-group, FP was more efficacious than nBUD in terms of mean morning PEF. Within the 2 mg nBUD sub-group, it can be stated that FP was at least efficacious as nBUD, since the confidence interval did not extend beyond  $151 \text{ min}^{-1}$  in favour of nBUD.

## SECONDARY EFFICACY PARAMETERS

### Diurnal Variation

The change from baseline in diurnal variation is shown in Table 4. The adjusted mean treatment difference (FB-nBUD) was -4.4 percentage points (p.p) ( $P=0.028$ , 95% CI [-8.4, -0.5]). Thus, FP was statistically significantly better at reducing diurnal variation than nBUD. Although the treatment difference was greater in the 2 mg nBUD patients than in the 4 mg nBUD patients (-5.9 p.p. vs -1.9 p.p.), there was no significance dose by treatment interaction, and thus no sub-group analyses were carried out for this parameter.

### Symptom-free 24-h Periods

During the pre-FP and nBUD baseline periods, the majority of patients (75% and 79% of patients, respectively) had no symptom-free days. After FP and nBUD treatment 67% and 87% of patients, respectively, did not experience any change in their symptom scores, 25% and 13% showed an improvement, and 8% and 0% worsened. The difference between treatments was not statistically significant ( $P=0.41$ ).

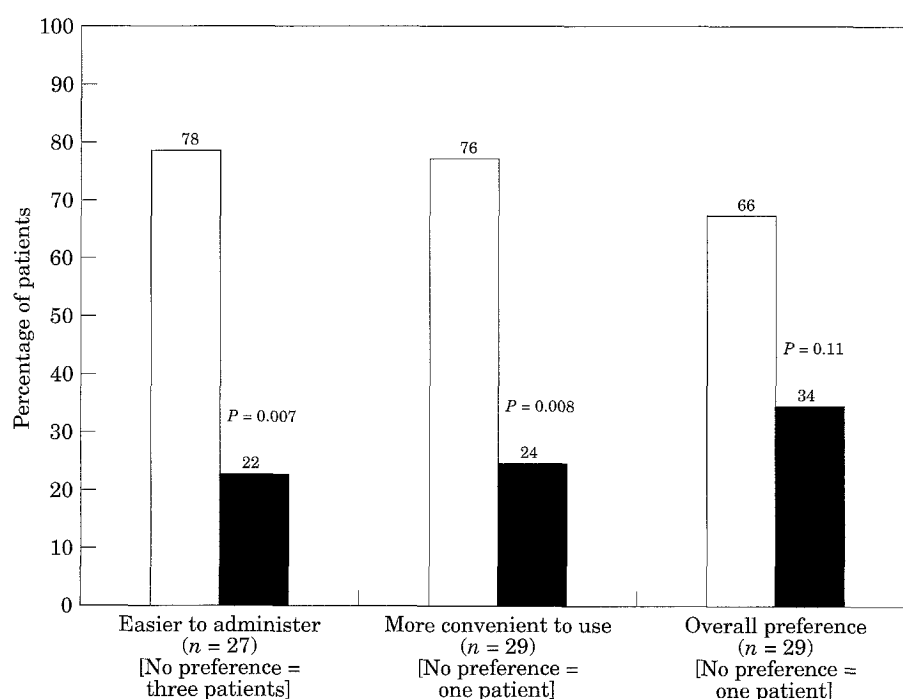


FIG. 4. Percentage of patients preferring each treatment for three treatment preference questions – all patients who completed the study ( $n=30$ ). For FP and BUD, the percentages were calculated of those patients who expressed a preference. Open bars, FP; solid bars, nBUD.

TABLE 5. Cost analysis

Type of medication	Fluticasone propionate ( <i>n</i> =24)	Treatment	
		Nebulized budesonide	
		2 mg ( <i>n</i> =16)	4 mg ( <i>n</i> =8)
Medication used during study			
Costs per patient	£77.57	£134.36	£272.06
Relative cost ratio per patient (nBUD/FP)		1.7	3.5

### Treatment Preference

The responses to the device preference questions are shown in Fig. 4. These data show strong evidence that patients considered FP via the MDI and Volumatic<sup>®</sup> both easier to administer ( $P=0.007$ ) and more convenient to use ( $P=0.008$ ). Of those patients who expressed an overall preference, 66% preferred FP via the MDI and Volumatic<sup>®</sup>, compared to 34% who preferred nBUD, although this difference was not statistically significant ( $P=0.11$ ).

### Cost Analysis

The asthma-related medication costs *excluding* study drug were similar during the FP and nBUD treatment periods, and between the two nBUD dose groups (around £50 per patient). The study drug costings are shown in Table 5. These show that the nBUD cost more than the FP.

### SAFETY

There were four serious adverse events reported by three patients, all of which occurred during the wash-out period when patients were receiving nBUD. Three of these were exacerbations of asthma which led to all three patients being hospitalized (two who had received FP in the first treatment period and one who had received nBUD previously). The fourth event was a lower respiratory tract infection. All resolved and were considered unlikely to be related or were not related to treatment.

Twelve patients reported a total of 21 minor adverse events whilst receiving FP, and 11 patients reported a total of 17 events during the nBUD treatment arm. The majority of these events were related to the lower respiratory tract and asthma.

### Discussion

Nebulized budesonide is not generally introduced for the treatment of asthma until other delivery methods and drugs have failed to keep the patient's condition under satisfactory control. It is an expensive and relatively complex form of therapy, both in terms of necessary equipment

and the kinetics of delivery of a drug in suspension. This study targeted the minority of severe asthmatics for whom regular nBUD appears to offer some benefit in maintaining asthma control, and tested whether FP 2 mg daily via an MDI and Volumatic<sup>®</sup> was clinically as effective in maintaining this level of control if substituted for nBUD.

To conform with current clinical practice, patients used their own nebulizers and compressors throughout the study. No attempt was made to standardize equipment or alter the usual maintenance checks undertaken by the patients. Previous studies have shown that different nebulizer/compressor combinations have different performances in terms of the flow rate produced at the nebulizer and the particle size profiles produced (3–5). Any variation in performance will have a direct effect on the amount of drug available to the lung, and therefore the actual dose the patient receives. For this reason, it was not the intention of this study to examine dose response, even though patients were nominally using two different doses of nBUD. A dose-response study would have required standardization of the delivery system.

In terms of the change in mean morning PEF, the primary parameter, FP was shown to be more efficacious than nBUD. The statistical analysis showed, however, that this treatment difference was affected by the dose of nBUD. A sub-group analysis showed, somewhat surprisingly, that the treatment difference in favour of FP was greater in patients who had received 4 mg nBUD than those who received 2 mg nBUD. Thus, FP was at least as efficacious as nBUD in the 2 mg sub-group, and significantly better in the 4 mg sub-group. It should, however, be noted that there were only eight patients in the nBUD 4 mg sub-group. The confidence interval in this group was very wide for this reason, and because of the wide variation in response.

The response in diurnal variation was not consistent with that seen for the change in mean morning PEF, as a greater improvement was seen in the 2 mg nBUD sub-group compared with the 4 mg nBUD sub-group, although it could be argued that the 2 mg nBUD sub-group had more room for improvement due to the higher baseline diurnal variation in this group.

There are several factors which need to be considered when interpreting these results. There were at least 17 different combinations of compressor and nebulizer used which could give rise to a large variability in the actual dose of budesonide which the patients received to the lung. The

effect of different fill volumes is also unclear. The longer inhalation time may have allowed more evaporation to occur at the higher dose, which could increase the viscosity of the suspension and possibly reduce the proportion of drug delivered to the lung. Individual responsiveness to fluticasone may be independent of responsiveness to budesonide. There may have been a difference in compliance between the two dose groups as patients in the higher budesonide dose group were required to take two ampoules twice a day compared to the one ampoule twice daily in the 2 mg group. However, compliance was not assessed formally in this study and indeed is extremely difficult to assess in clinical practice.

Patient preference for a particular drug and device combination is another aspect of management which is likely to affect compliance. In this study, the aim was to compare the patient's current nBUD regimen with the replacement of budesonide by FP. Patients did not discontinue nebulizer use during FP treatment since they continued nebulized bronchodilator therapy. Despite use of the MDI and Volumatic<sup>™</sup> as an additional device, more than three times as many patients found it easier and more convenient to administer FP by this route, than budesonide by nebulization. Although almost twice as many patients preferred FP via the MDI and Volumatic<sup>™</sup> to nBUD overall, this difference did not reach statistical significance. This was a more general and subjective question, and it is possible that patients took into consideration any previous beneficial experience of a nebulizer and may thus have had a pre-conception of benefit from this device.

Cost, as well as additional benefit, of a new treatment or regimen must be taken into consideration before it can be proposed as a viable alternative to a current treatment. On a per patient cost basis, the 2 mg nBUD used during the study treatment period was 1.7 times more expensive than the FP treatment, and for 4 mg nBUD this ratio increased to 3.5. This differential would be even larger if the cost of the nebulizer equipment and maintenance were taken into consideration.

In conclusion, FP 2 mg daily via the MDI and Volumatic<sup>™</sup> has been shown to be at least as efficacious as, and less expensive than, either 2 or 4 mg daily nBUD. Fluticasone propionate via the MDI and Volumatic<sup>™</sup> may, therefore, offer an alternative to nBUD in those patients who have been deemed to require such therapy, with the advantages of being cheaper, simpler and in a more standardized form of delivery than nBUD.

## Acknowledgements

The authors would like to thank the following who participated in the study: Dr H. W. Clague, Bishop Auckland, Co. Durham; Dr S. W. Clarke, London; Dr A. M. P. East, Poulton-Le-Fylde, Lancashire; and Dr A. R. H. Warley, Salisbury, Wiltshire. This study was sponsored by GlaxoWellcome U.K. Ltd. Volumatic<sup>™</sup> and Flixotide<sup>™</sup> are trademarks of the GlaxoWellcome Group of companies. Pulmicort Respules<sup>™</sup>, are a trademark of Astra.

## References

- Otulana BA, Varma N, Bullock A *et al.* High dose nebulised steroid in the treatment of chronic steroid-dependent asthma. *Respir Med* 1992; **86**: 105–108.
- Higenbottam TW, Clark RA, Luksa AR *et al.* The role of nebulised budesonide in permitting a reduction in the dose of oral steroid in persistent severe asthma. *Eur J Clin Res* 1994; **5**: 1–10.
- Smith EC, Denyer J, Kendrick AH. Comparison of twenty three nebulizer/compressor combinations for domiciliary use. *Eur Respir J* 1995; **8**: 1214–1221.
- Newnham DM, Lipworth BJ. Nebuliser performance, pharmacokinetics, airways and systemic effects of salbutamol given via a novel nebuliser delivery system ('Ventstream'). *Thorax* 1994; **49**: 762–770.
- Hardy JG, Newman SP, Knoch M. Lung deposition from four nebulisers. *Respir Med* 1995; **87**: 461–465.
- Barnes NC, Marone G, Di Maria GU *et al.* A comparison of fluticasone propionate, 1 mg daily, with beclomethasone dipropionate, 2 mg daily, in the treatment of severe asthma. *Eur Respir J* 1993; **6**: 877–884.
- Leblanc P, Mink S, Keistinen T *et al.* A comparison of fluticasone propionate 200 µg/day with beclomethasone dipropionate 400 µg/day in adult asthma. *Allergy* 1994; **49**: 380–385.
- Lundback B, Alexander M, Day J *et al.* Evaluation of fluticasone propionate (500 µg day<sup>-1</sup>) administered either as a dry powder via a Diskhaler<sup>®</sup> inhaler or pressurized inhaler and compared with beclomethasone dipropionate (1000 µg day<sup>-1</sup>) administered by pressurized inhaler. *Respir Med* 1993; **87**: 609–620.
- Fabbri L, Burge PS, Croonenborgh L *et al.* Comparison of fluticasone propionate with beclomethasone dipropionate in moderate to severe asthma treated for one year. *Thorax* 1993; **48**: 817–823.
- Connolly A. A comparison of fluticasone propionate 100 µg twice daily with budesonide 200 µg twice daily via their respective powder devices in the treatment of mild asthma. *Eur J Clin Res* 1995; **7**: 15–29.
- Langdon CG, Thompson J. A multicentre study to compare the efficacy and safety of inhaled fluticasone propionate and budesonide via metered-dose inhalers in adults with mild to moderate asthma. *Br J Clin Res* 1994; **5**: 73–84.
- Langdon CG, Capsey LJ. Fluticasone propionate and budesonide in adult asthmatics – a comparison using dry-powder inhaler devices. *Br J Clin Res* 1994; **5**: 85–99.
- Ayres JG, Bateman ED, Lundback B *et al.* High dose fluticasone propionate, 1 mg daily, *versus* fluticasone propionate 2 mg daily, or budesonide, 1.6 mg daily, in patients with chronic severe asthma. *Eur Respir J* 1995; **8**: 579–586.
- Jones B, Kenward MG. *Design and Analysis of Cross-over Trials*. Chapman and Hall, 1990.